REMARKS

Amendments in the claims

Following amendment as requested herein, Claims 1, 3-4, and 14-24 are pending in the present application, of which Claims 19 and 20 were previously withdrawn and Claim 2 was previously canceled. Claims 5-13 are canceled by present amendment. Claims 21-24 are new claims.

Claim 1 is amended to further enhance clarity by reciting "identifying a subject without clinically confirmed Parkinson's disease". This amendment is supported throughout the specification as filed, for example, at **[0003]** on p. 1. Claim 1 is further amended, without prejudice, to focus the present application on an embodiment of the invention wherein the administering step is drawn to administering rotigotine or a physiologically acceptable salt thereof. See, for example, the specification as filed at least at paragraph **[0040]** and originally filed Claim 12. This amendment is requested in the interest of advancing prosecution by reducing the number of issues in examination. No admission is made that the claim as previously presented, reciting an art-recognized genus of compounds is not patentable, and Applicant reserves the right to reintroduce presently canceled subject matter in a later filed continuation application.

Claim 3 is amended to align the wording more closely with that of herein-amended Claim 1. Support for such is also found in the specification as filed at least at paragraphs **[0046]** and **[0049]**.

Claim 15 is amended to clarify that the subject has a UPDRS motor score of less than 10 before administering rotigotine. Support for this amendment is found in the specification as filed at least at paragraph **[0054]**.

Cancellation of Claims 5-13 and amendment of Claims 17-18 are necessitated by amendment of Claim 1 as proposed above.

Opportunity has also been taken, in amending the claims, to correct typographical errors or to rephrase where it has been desirable to do so for enhanced clarity or eliminate redundancy (*e.g.* Claims 4, 14, and 15). Such amendments are permissible under MPEP §2163.07, and are not intended to affect the scope of the claims.

New Claim 21 depends from Claim 1 and recites "wherein the subject has one, two or

three symptoms selected from the group consisting of rigor, resting tremor, bradykinesia and postural instability, to a partial degree." Claim 21 is supported throughout the specification as filed and, for example, by originally-filed Claim 2.

New Claim 22 recites a method for preventive treatment of Parkinson's disease by identifying a subject without symptoms of Parkinson's disease but with an increased risk of developing Parkinson's disease and administering to the subject rotigotine or a physiologically acceptable salt thereof. Both steps were explicit in the body of Claim 1 prior to amendment herein; the "administering" step was explicit in originally-filed Claim 13 and the step of "identifying a subject without symptoms of Parkinson's disease but with an increased risk of developing Parkinson's disease" was explicit in originally-filed Claim 2. The specification as filed is also replete with disclosure as to how such a subject can be identified and administering rotigotine or a physiologically acceptable salt. See, for example, paragraphs **[0038]–[0054]** (specifically, at least at paragraphs **[0040]**, **[0041]** and **[0044]**) of the specification as filed.

New Claim 23 recites a method for preventive treatment of Parkinson's disease wherein the subject displays a mutation in a PARK gene and/or a modification to alpha synuclein or neuromelanin pattern. The subject displaying a mutation in a PARK gene and/or a modification to alpha synuclein or neuromelanin pattern was explicit in originally-filed Claim 4. The specification as filed also supports such new claim at least at paragraphs **[0045]** and **[0047]**.

New Claim 24 is recites a method for preventive treatment of Parkinson's disease wherein the subject displays a dopaminergic cell loss in substantia nigra of less than 50% before administering rotigotine. Support for such dopaminergic cell loss is found in the specification as filed at least at paragraph **[0051]**.

New Claims 21-24 are drawn to a method for preventive treatment of Parkinson's disease or Group I, the presently elected group.

No new matter is added, and no change of inventorship is believed to result from the amendment of claims as proposed herein.

RESPONSE TO OFFICE ACTION DATED 14 SEPTEMBER 2009

1. Rejection under 35 U.S.C. §102(b) over Tuite

Claims 1, 5–14, 17 and 18 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Tuite & Riss (2003) Expert Opin. Invest. Drugs 12(8):1335–1352 (herein "Tuite"). This rejection is respectfully traversed.

At the outset, it is noted that the publication date of Tuite (2003) is less than one year before the earliest priority date of the present application (24 December 2003). Tuite does not constitute statutory prior art under 35 U.S.C. §102(b), and no admission is made herein that the disclosure of Tuite constitutes prior art to the present invention under any section of 35 U.S.C. §102. Applicant reserves the right to make a showing of earlier invention to disqualify Tuite. However, such a showing is unnecessary, as even if Tuite represented prior art to the present invention, Tuite would not anticipate the present claims, for reasons set forth below.

1.1. No Teaching or Disclosure of Subjects Without Clinically Confirmed Parkinson's Disease

Anticipation of a claim under 35 U.S.C. §102 requires that every limitation of the claim is disclosed, expressly or inherently, in the cited document. This is not the case here. Tuite fails to disclose a method for preventive treatment of Parkinson's disease by "identifying a subject without clinically confirmed Parkinson's disease."

As acknowledged by the Examiner, Tuite reviews a clinical trial of rotigotine administered transdermally in 316 patients diagnosed with early stage Parkinson's disease (de novo patients or otherwise). Therefore, Tuite's patients had clinically confirmed Parkinson's disease, and would therefore exhibit at least two of the four cardinal symptoms of Parkinson's disease (falling outside of the definition of "individuals with early symptoms of Parkinson's disease" as set forth in Applicant's specification at paragraph **[0046]**). In contrast, the subject according to Claim 1 has not (or not yet) been diagnosed with Parkinson's disease, even "early stage" Parkinson's disease, and does not fully exhibit two of the four cardinal symptoms of Parkinson's disease. Therefore, Claim 1 is novel over Tuite.

Claims 14, 17 and 18 depend from and incorporate all limitations of Claim 1 and are accordingly novel over Tuite for at least the same reasons that Claim 1 is novel. Claims 5-13 are canceled by present amendment, and thus, such rejection of Claims 5-13 is moot.

1.2. No Teaching or Disclosure Of Less Than 60% Dopaminergic Neuron Loss

Claim 14 embodies all of the limitations of Claim 1 and is therefore novel over Tuite for at least the reason presented in Sec. 1.1. However, for the record, Applicant is addressing the Examiner's argument that the limitation of "a dopaminergic cell loss in the substantia nigra of less than 60%" is inherently anticipated by Tuite as evidenced by Becker *et al.* (2002) J. Neurol. 249(Suppl. 3):III/40–III/48 (herein "Becker"). Becker reports that "approximately 60% of the nigrostriatal neurons of the substantia nigra are degenerated before neurologists can establish the diagnosis" (Office Action, p. 5, lines 5-7).

The assertion in the Office Action (Office Action, p. 5, lines 7-9) that

> [a]ccordingly, all the individuals in the study recited by Tuite who had early stages of PD inherently had approximately 60% loss of the substantia nigra

is not logical. It is illogical to conclude that every patient reviewed by Tuite would have had "less than 60% loss" of substantia nigra. In fact, the weight of the evidence of record suggests that patients with clinically confirmed classical or idiopathic Parkinson's disease, like the patients reviewed by Tuite, have greater than 60% dopaminergic neuron loss in the substantia nigra. For example:

- The specification as filed states "patients with Parkinson's disease only develop the motor disturbances once approximately 70% to 80% of the dopaminergic neuron[]s in the substantia nigra (SN) have been irreversibly damaged." *See* specification as filed at paragraph **[0003]**.
- As admitted in the present Office Action at p. 14, lines 15–20, International Patent Publication No. WO 02/31499 (herein "Double") states that in classical or idiopathic Parkinson's disease at least 65% of dopaminergic neurons in the substantia nigra are lost prior to clinical onset typified by the motor symptom triad of tremor, rigidity and bradykinesia.

Accordingly, it does not follow that **all** of the subjects reviewed by Tuite, with clinically confirmed Parkinson's disease, would have had **less than** 60% loss of substantia nigra (as recited in Claim 14). For at least these reasons, Claim 14 is not inherently or expressly anticipated by the subjects in the study reviewed by Tuite.

Withdrawal of the present rejection under 35 U.S.C. §102(b) over Tuite is respectfully requested.

2. Rejection under 35 U.S.C. §102(b) over Shoulson

Claims 1, 5-13, and 15-18 are rejected under 35 U.S.C. §102(b) as allegedly anticipated by Parkinson Study Group (2003) Arch. Neurol. 60:1721–1728 (referenced in the Office Action and below as "Shoulson"). This rejection is respectfully traversed.

At the outset, it is noted that the publication date of Shoulson (December 2003) is less than one year before the earliest priority date of the present application (24 December 2003). Shoulson does not constitute statutory prior art under 35 U.S.C. §102(b), and no admission is made herein that the disclosure of Shoulson constitutes prior art to the present invention under any section of 35 U.S.C. §102. Applicant reserves the right to make a showing of earlier invention to disqualify Shoulson. However, such a showing is unnecessary, as even if Shoulson represented prior art to the present invention, Shoulson would not anticipate the present claims, for reasons set forth below.

2.1. No Teaching or Disclosure of Subjects Without Clinically Confirmed Parkinson's Disease

Anticipation of a claim under 35 U.S.C. §102 requires that every limitation of the claim is disclosed, expressly or inherently, in the cited document. That is not the case here. Shoulson fails to disclose a method for preventive treatment of Parkinson's disease by "identifying a subject without clinically confirmed Parkinson's disease."

Shoulson reports a clinical trial of rotigotine applied transdermally in 242 patients. Shoulson (p. 1722, emphasis added) states the eligible subjects included those who "were diagnosed as having idiopathic PD and a Hoehn and Yahr stage of 3 or less." Therefore, Shoulson's patients had clinically confirmed Parkinson's disease, and would therefore exhibit at least two of the four cardinal symptoms of Parkinson's disease (falling outside of the definition of "individuals with early symptoms of Parkinson's disease" as set forth in Applicant's specification at paragraph **[0046]**). In contrast, the subject according to Claim 1 has not (or not yet) been diagnosed with Parkinson's disease, even "early stage" Parkinson's disease, and does not fully exhibit two of the four cardinal symptoms of Parkinson's disease. Therefore, Claim 1 is novel over Shoulson.

> Furthermore, to clarify for the record, the Office Action (p. 7, lines 16-20) alleges that
>
> applicants define in Table 2, that a Hahn's score of less than 3 have very mild bilateral or unilateral disease...[and] [a]s such it is implicit that the subject population in Shoulson's study, fall under instantly defined parameters as recited above and therefore the instant claims are anticipated by [] Shoulson.

At the outset, the subjects in Shoulson were identified as those that 1) had clinically diagnosed Parkinson's disease and 2) that had a Hoehn and Yahr score of 3 or less. *See* Shoulson, p. 1722. As articulated above, Claim 1 is drawn to subjects without clinically confirmed Parkinson's disease. Thus, no matter what the Hoehn and Yahr score was of the subjects, the subjects with clinically confirmed Parkinson's disease reported on by Shoulson do not "fall under [the] instantly defined parameters".

Claims 14 and 15–18 depend from and incorporate all limitations of Claim 1 and are accordingly novel over Shoulson for at least the same reasons that Claim 1 is novel. Claims 5-13 are canceled by present amendment and thus, such rejection of Claims 5-13 is moot.

2.2. No Teaching Or Disclosure of Less Than 60% Dopaminergic Cell Loss

With particular reference to Claim 14, the Examiner again argues that the limitation of "a dopaminergic cell loss in the substantia nigra of less than 60%" as recited therein renders the claim inherently anticipated by Shoulson as evidenced by Becker. Becker reports that "approximately 60% of the nigrostriatal neurons of the substantia nigra are degenerated before neurologists can establish the diagnosis" (Office Action, p. 8, lines 21-22 – p. 9, line 1). Applicant is uncertain why this line of argument is included, as Claim 14 is not rejected under 35 U.S.C §102(b) in view of Shoulson. Regardless, Claim 14 is novel over Shoulson in view of Becker for the same reasons presented in Section 1.2 above.

Withdrawal of the present rejection under 35 U.S.C. §102(b) over Shoulson is respectfully requested

3. Rejection under 35 U.S.C. §103(a) over Tuite, as evidenced by Becker, in view of Double and Guttman

Claims 1 and 3-18 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Tuite as evidenced by Becker, in view of Double and Guttman *et al.* (2003) Can. Med. Assoc. J. 168:293–301 (herein "Guttman"). This rejection is respectfully traversed.

In addition to Tuite (*see supra* Section 1), the publication date of Guttman (Feb. 4, 2003) is less than one year before the earliest priority date of the present application (December 24, 2003). Tuite and Guttman do not constitute statutory prior art under 35 U.S.C. §102(b), and no admission is made herein that the disclosure of Tuite and Guttman constitute prior art to the present invention under any section of 35 U.S.C. §102. Applicant reserves the right to make a showing of earlier invention to disqualify Tuite and Guttman. However, such a showing is unnecessary, as even if Tuite and Guttman represented prior art to the present invention, Tuite and Guttman, alone or in combination with Double and Becker, do not render obvious the present claims, for reasons set forth below.

3.1 No Teaching of Preventing Parkinson's Disease With Rotigotine

None of the cited documents teach or suggest a method for preventing Parkinson's disease, much less preventing Parkinson's disease in a patient population not clinically diagnosed with Parkinson's disease. Tuite and Guttman deal with the treatment of symptoms of Parkinson's disease in clinically confirmed Parkinson's disease patients. Becker states: "...the identification of patients at risk and at earlier stages of the disease appears to be essential for any successful neuroprotection". However, despite Becker stating such a need to identify patients at risk, Becker:

1. fails to suggest or teach any available therapeutic options, much less use of rotigotine, for prevention of Parkinson's disease;
2. states "[a]t present, no treatment has proven to influence this progressive course of the disease by protecting neurons or by postponing cell death"; and
3. concludes "at present we have no therapeutic options for these subjects and, if we had any, different indications for early intervention would have to be established. *See* Becker, at p. III/40, III/45.

Further, this deficiency (or failure to teach a method of preventing Parkinson's disease) is not cured by Double. Double provides a method for detecting preclinical Parkinson's disease but does not teach or suggest that such an individual is a suitable case for treatment with a dopamine agonist such as rotigotine to prevent Parkinson's disease. Double instead proposes treatment of a subject that tested positive, including "administering a therapeutically effective amount of at least one of the following: antioxidants, iron chelators, nonamine [*sic*;

monoamine?] oxidase inhibitors, apoptosis inhibitors, growth factors, dopamine receptor inhibitors, endogenous enzymes which protect against oxidative damage such as glutathione, superoxide dismutase and catalase, inhibitors of excitatory damage, zonisamide, benzamide compounds, ethanesulfonyl-piperidine derivatives, or a combination thereof" (Double, p. 3, lines 24–30, emphasis added). Double provides no mention of preventing Parkinson's disease by administering a dopamine agonist, much less rotigotine, to a subject who does not have clinically confirmed Parkinson's disease. In fact, Double mentions the opposite of dopamine agonists, dopamine receptor inhibitors. For at least these reasons, the combination of Tuite, evidenced by Becker, in view of Double and Guttman fails to teach, disclose, or suggest a method for preventing Parkinson's disease, including by administering rotigotine.

All claim limitations must be considered in judging the patentability of a claim against the prior art. *See* MPEP 2143.03, *citing In re* Wilson, 424 F.2d 1382, 165 USPQ 494 (CCPA 1970). If a reference is missing claimed features, there must be some apparent reason either in the reference or the general knowledge in the art to modify the reference to include the missing subject matter. *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ 1385 (2007).

3.2 No Rationale to Modify the alleged Combination for Preventive treatment of Parkinson's Disease

The Examiner's asserted rationale is

> [i]t would have been obvious to one of ordinary skill in the art to employ rotigotine in prophylactic treatment of Parkinson's disease because rotigotine is effective for the treatment of Parkinson's disease as taught by Tuite et al **early stages of the disease**. (Office Action, p. 15, emphasis in original)

First, as stated above, Tuite's patient population is different from Applicant's claimed patient population. Unlike Tuite, Applicant's patient population does not have clinically confirmed Parkinson's disease, regardless of what stage in the progression of the disease. None of the secondary references teach any effective preventive treatment, thus there is no motivation or suggestion to modify Tuite for preventive treatment.

Second, just because a drug (such as rotigotine) is known to alleviate symptoms of clinical Parkinson's disease is no reason to believe it can successfully be used for prevention

of Parkinson's disease. Symptomatic treatment and prevention of a disease are drastically different. For example, Rascol (2002) 359:1589-98 reports that "[a]mong the randomized controlled trials done to test neuroprotection in Parkinson's disease with [symptomatic] drugs such as tocopherol, selegiline, or bromocriptine, none produced definite evidence for neuroprotection." There is no reason to believe that a drug which treats a symptom would provide disease modification. Thus, why would one of ordinary skill in the art modify Tuite for prevention of Parkinson's disease, especially in patients without clinically confirmed Parkinson's disease – and in light of Double's teaching away? (Double proposes treatment, not prevention, with "dopamine receptor inhibitors" as opposed to a dopamine receptor agonists.).

Accordingly, there is a lack of motivation to combine Tuite, as evidenced by Becker, with Guttman and Double, or administer rotigotine prophylactically to subjects in a pre-diagnostic state.

3.3 Prophylactic Treatment of Parkinson's Disease is Admittedly Unpredictable

Even if a rationale existed to select and modify elements from the cited documents (which is not admitted herein), the Examiner appears to be applying the "obvious to try" standard in making the present rejection.

The Examiner (p. 17) states:

> As stated by Applicant, prophylactic treatment methods for Parkinson's disease are still unpredictable and there are no therapies available currently which delay the progression of PD. This fact in itself, supported by the positive results shown by Tuite in early stage PD treatment would motivate an artisan skilled in the pharmaceutical arts to test if the rotigotine would provide any prophylactic benefits. (emphasis added)

However, there has to be "a finite number of identified, predictable solutions" to establish a presumption of *prima facie* obviousness. *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) (emphasis added). The unpredictability of prophylactic treatment of Parkinson's disease is an implicit admission by the Office that there is not "a finite number of identified, predictable solutions." For example, one of skill in the art would have to:

1. select one of the numerous drugs known to be effective in treating symptoms

associated with Parkinson's disease (with no pattern of preference or guidance),

2. determine if the selected drug had a neuroprotective effect, and
3. determine the effect of treating subjects without clinically confirmed Parkinson's disease.

Finding a drug that met all 3 categories could involve an infinite number of investigations and experimentations. Thus, the cited documents provide no more than a "plan" or "invitation" for those of skill in the art to experiment. *See* MPEP 2164.06(b).

Further, it appears the Examiner is using "unpredictability" in prophylaxis of Parkinson's disease to prove an "obvious to try" argument in order to sustain a presumption of *prima facie* obviousness. To the contrary, unpredictability is a factor used to prove that no *prima facie* obviousness could exist.

Unpredictability in prophylaxis of Parkinson's disease is further supported by:

- Nair *et al.* Biochem. J. 373:25-32 (2003) (emphasis added) which states that "certain DA agonists, **but not all**, could induce a robust increase in cell survival via activation of the D_2 receptors";
- Becker by stating that "[a]t present, no treatment has proven to influence this progressive course of the disease by protecting neurons or by postponing cell death."; and
- Guttman (p. 297, bottom Col. 1) emphasizes that "no therapies are proven to ... delay the progression of Parkinson's disease."

This evidence suggests that the "likely" outcome that exists in the art leads the person of ordinary skill to have an expectation of failure, rather than an expectation of success. (Applicant stresses that the standard for nonobviousness is not expectation of failure, but lack of reasonable expectation of success. A showing of expectation of failure just makes the case for nonobviousness stronger.)

In this unpredictable, complex art, Applicant was the first to identify rotigotine as a 1) a neuroprotective agent and 2) effective for preventative treatment of Parkinson's disease in subjects without clinically confirmed Parkinson's disease. Accordingly, it could not have been predicted that rotigotine, although known to be effective in reducing symptoms of Parkinson's disease post-diagnosis, would prevent Parkinson's disease in subjects without

clinically confirmed Parkinson's disease.

3.4 Conclusion: Rejection Under 35 U.S.C. § 103

Each of Claims 3-4 and 14-18 depends from and incorporates all limitations of Claim 1. Notwithstanding the Examiner's comments with regard to specific dependent claims, each of Claims 3-4 and 14-18 is non-obvious over the cited art for at least the same reasons that Claim 1 is non-obvious. Claims 5-13 are presently canceled, and thus, such rejection for Claims 5-13 is moot.

Withdrawal of the present rejection under 35 U.S.C. §103(a) over Tuite as evidenced by Becker, in view of Double and Guttman, is respectfully requested.

4. Rejection under 35 U.S.C. §103(a) over Shoulson, as evidenced by Becker, in view of Double and Guttman

Claims 1 and 3-18 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Shoulson as evidenced by Becker, in view of Double and Guttman. This rejection is respectfully traversed.

As articulated more fully above (*see supra* Sections 2 and 3), Shoulson and Guttman do not constitute statutory prior art under 35 U.S.C. §102(b), and no admission is made herein that the disclosure of Shoulson and Guttman constitute prior art to the present invention under any section of 35 U.S.C. §102. Applicant reserves the right to make a showing of earlier invention to disqualify Shoulson and Guttman. However, such a showing is unnecessary, as even if Shoulson and Guttman represented prior art to the present invention, Shoulson and Guttman, alone or in combination with Double and Becker, do not render obvious the present claims, for reasons set forth below.

4.1 No Teaching of Preventing Parkinson's Disease With Rotigotine

As articulated more fully above (see Section 3.1), Double and Guttman fail to teach, disclose, or suggest a method for preventing Parkinson's disease by administering rotigotine. Shoulson, as evidenced by Becker, does not cure the deficiency, as it also fails to teach or suggest administering rotigotine for the prevention of Parkinson's disease.

4.2 No Rationale to Modify the alleged Combination for Preventive treatment of Parkinson's Disease

The Examiner's asserted rationale is

> [i]t would have been obvious to one of ordinary skill in the art to employ rotigotine in prophylactic treatment of Parkinson's disease because rotigotine is effective for the treatment of Parkinson's disease as taught by Shoulson et al **early stages of the disease**. (Office Action, p. 15, emphasis in original)

First, as stated above, Shoulson's patient population is different from Applicant's claimed patient population. Unlike Shoulson, Applicant's patient population does not have clinically confirmed Parkinson's disease, regardless of what stage in the progression of the disease. None of the secondary references teach any effective preventive treatment, thus there is no motivation or suggestion to modify Shoulson for preventive treatment.

Second, as stated above, just because a drug (such as rotigotine) is known to alleviate symptoms of clinical Parkinson's disease is no reason to believe it can successfully be used for prevention of Parkinson's disease. Symptomatic treatment and prevention of a disease are drastically different. For example, Rascol (2002) 359:1589-98 reports that "[a]mong the randomized controlled trials done to test neuroprotection in Parkinson's disease with [symptomatic] drugs such as tocopherol, selegiline, or bromocriptine, none produced definite evidence for neuroprotection." There is no reason to believe that a drug which treats a symptom would provide disease modification. Thus why would one of ordinary skill in the art modify Shoulson for prevention of Parkinson's disease, especially in patients without clinically confirmed Parkinson's disease – and in light of Double's teaching away? (Double proposes treatment, not prevention, with "dopamine receptor inhibitors" as opposed to a dopamine receptor agonist.)

Accordingly, there is a lack of motivation to combine Shoulson, as evidenced by Becker, with Guttman and Double, or administer rotigotine prophylactically to subjects in a pre-diagnostic state.

4.3 Prophylactic Treatment of Parkinson's Disease is Admittedly Unpredictable

Even if a rationale existed to select and modify elements from the cited documents (which is not admitted herein), the Examiner appears to be applying the "obvious to try" standard in making the present rejection.

The Examiner (p. 24) states:

> As stated by Applicant, prophylactic treatment methods for Parkinson's disease are still unpredictable and there are no therapies available currently which delay the progression of PD. This fact in itself, supported by the positive results shown by Shoulson in early stage PD treatment would motivate an artisan skilled in the pharmaceutical arts to test if the rotigotine would provide any prophylactic benefits.

However, there has to be "a finite number of identified, predictable solutions" to establish a presumption of *prima facie* obviousness. *KSR International Co. v. Teleflex Inc.*, 127 S.Ct. 1727, 82 USPQ2d 1385 (2007) (emphasis added). The unpredictability of prophylactic treatment of Parkinson's disease is an implicit admission by the Office that there is not "a finite number of identified, predictable solutions." As stated above more fully, selecting one of the numerous drugs known to be effective in treating symptoms associated with Parkinson's disease (with no pattern of preference or guidance), determining if the selected drug had a neuroprotective effect, and determining the effect of treating subjects without clinically confirmed Parkinson's disease could involve an infinite number of investigations and experimentations. Thus, the cited documents provide no more than a "plan" or "invitation" for those of ordinary skill in the art to experiment. *See* MPEP 2164.06(b).

As also stated more fully above, unpredictability of prophylaxis of Parkinson's disease is further supported by the weight of evidence of record. *See* Nair *et al.* Biochem. J. 373:25-32 (2003) (emphasis added) ("certain DA agonists, but not all, could induce a robust increase in cell survival via activation of the D_2 receptors"); *see also* Becker ("[a]t present, no treatment has proven to influence this progressive course of the disease by protecting neurons or by postponing cell death"). This evidence suggests that the "likely" outcome that exists in the art leads the person of ordinary skill to have an expectation of failure, rather than an expectation of success. (Applicant stresses that the standard for nonobviousness is not expectation of failure, but lack of reasonable expectation of success. A showing of expectation of failure just makes the case for nonobviousness stronger.)

That is until Applicant's invention. Applicant was the first to 1) identify rotigotine as a neuroprotective agent and 2) that it was effective for preventative treatment of Parkinson's disease in subjects without clinically confirmed Parkinson's disease. Accordingly, it could not have been predicted that rotigotine, although known to be effective in reducing symptoms

of Parkinson's disease post-diagnosis, would prevent Parkinson's disease in subjects without clinically confirmed Parkinson's disease.

4.4 Conclusion: Rejection Under 35 U.S.C. § 103

Each of Claims 3-4 and 14-18 depends from and incorporates all limitations of Claim 1. Notwithstanding the Examiner's comments with regard to specific dependent claims, each of Claims 3-4 and 14-18 is non-obvious over the cited art for at least the same reasons that Claim 1 is non-obvious. Claims 5-13 are canceled by present amendment and thus, such rejection is moot for claim 5-13.

Withdrawal of the present rejection under 35 U.S.C. §103(a) over Shoulson as evidenced by Becker, in view of Double and Guttman, is respectfully requested.

5. Double patenting with respect to co-pending applications

Claims 1 and 3-18 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 15-24 of co-pending application Serial No. 11/060,997 (Office Action, p. 25-26). This rejection is provisional because the allegedly conflicting claims have not yet been patented. The Examiner's statement that "[t]he subject matter claimed in the instant application...would be covered by any patent granted on that copending application" (Office Action, p. 25) is not a conclusion that can be reliably drawn at the present time. Applicant may elect to argue to overcome any or all of these grounds of rejection or provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the reference application issues as a patent.

Claims 1, 5-13 and 17-18 are provisionally rejected under the judicially-created doctrine of obviousness-type double patenting as allegedly unpatentable over Claims 8, 11, and 14 of co-pending application Serial No. 10/593,964 (Office Action, p. 26-27). This rejection is provisional because the allegedly conflicting claims have not yet been patented. The Examiner's statement that "[t]he subject matter claimed in the instant application...would be covered by any patent granted on that copending application" (Office Action, p. 26) is not a conclusion that can be reliably drawn at the present time. Applicant may elect to argue to overcome any or all of these grounds of rejection or provide a terminal disclaimer (to the extent necessary) once the present claims have been found to be otherwise allowable and/or once the

reference application issues as a patent.

6. Conclusion

It is believed that all of the stated grounds of rejection are properly traversed, accommodated, or rendered moot herein. Applicant therefore respectfully requests that the Examiner reconsider and withdraw all presently outstanding rejections. It is believed that a full and complete response has been made to the present Office Action and that the application is in condition for allowance. Should any issues remain, the Examiner is invited to call the undersigned at the telephone number given below.